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FORMULATION AND *IN-VITRO* EVALUATION OF ULTRA-DEFORMABLE VESICULAR GEL OF ETODOLAC

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Abstract:

Transferosome is an ultra-deformable, highly flexible and stress-responsive complex system which consists of aqueous core surrounded composite lipid bilayer. Due to their resizing and self- optimized property, they are able to deliver low as well as high molecular weight into or through the skin. The main objective of this study is to prepare etodolac loaded transfersomes for the treatment of osteoarthritis. The dispersion of Etodolac loaded transfersomes was prepared by changing the ratio of surfactant and phospholipid by thin film hydration method. Prepared transferosme of Etodolac was optimized on the basis of various in-vitro evaluation characteristics such as zeta potential, TEM, etc. Optimized transferosome were further converted to Gel by using various concentrations of containing Carbopol 934. All gel formulations were evaluated for spreadability, extrudability, viscosity, pH, in vitro diffusion, stability study and found good results. From the % drug release kinetics study it was concluded that formulation follows zero order kinetics.

Keywords: *Transfersomes, Gel, Etodolac, Zeta potential, TEM, Entrapment efficiency.*

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INTRODUCTION:

Transdermal patches are developed in the 1970s and the first patch was approved in 1979 by FDA in the treatment of motion sickness. Scopolamine is the first drug that is incorporated and in 1981 patches for nitroglycerine were approved [1]. The development of a novel vesicular system for the present drug has been increased in the past few years. This development increases safety, efficacy, and also patient compliance. Today various patches are available such as clonidine, nitroglycerine, nicotine, testosterone, etc. In transdermal drug delivery, hepatic first-pass metabolism is eliminated which minimizes side effects of drug cause by temporary overdose. In the coming years, one of the most common methods for drug delivery will be through the skin. Physical and chemical penetration enhancers have been shown to be effective in improving medication penetration through the skin in studies. The focus should be on skin irritation, to select penetration enhancers that possess optimum enhancement with minimal skin irritation [2, 11].

Table 1: Comparison of transdermal route with other routes

Factors	Intra vascular route	Oral route	Transdermal route
Reduce first pass effect	Yes	No	Yes
Constant drug release	Yes	No	Yes
Self-administration	No	Yes	Yes

The name "Transfersomes" comes from the Latin word "Transferre," which means "to convey across," and the Greek word "some," which means "body". Transfersomes was developed in 1991 by Gregor Ceve [3,4]. Liposomes and niosomes have several issues such as poor skin permeability, their permeation nature, their aggregation, and fusion in skin tissue which are not suitable for transdermal drug delivery. Hence it leads to the development of a new system known as “Transfersomes”. Recent research also shows that it has the potential to transfer vaccines, steroids, proteins, and peptides across the skin. Transfersomes are also used for transporting genetic material and achieving transfection [5].

Transfersomes is an ultradeformable, highly flexible, and stress-responsive complex system which consists of an aqueous core surrounded by a composite lipid bilayer. It is a novel, elastic, or ultradeformable vesicular drug carrier system composed of phospholipids, surfactant, and dihydrogen monoxide for enhanced transdermal drug distribution [6]. Transfersomes resize themselves with the intracellular sealing lipid of the stratum corneum to overcome filtration and skin penetration difficulty. Due to their resizing and self-optimized property, they can deliver low as well as high molecular weight into or through the skin. The resizing property of transfersomes reduces the risk of vesicular rupture in the skin. The flexibility of Transfersomes depends on the type of lipid, surfactant, and different lipid concentrations [7].

Table 2: Different additives used in formulation of Transfersomes [8,9]

Sr. No.	Class	Example	Use
1	Phospholipid	Soya phosphatidyl choline, egg phosphatidyl choline, dipalmitoyl phosphatidyl choline	Vesicle forming component
2	Surfactant	Tween 80, Span 60, Tween 40, Tween 20, Sodium cholate	Vesicle forming component
3	Solvents	Methanol, Ethanol, Chloroform, Isopropyl alcohol	Solvent
4	Buffering agents	Saline phosphate buffer (pH 7.4)	Hydrating medium
5	Dye	Rhodamine-123, Rhoda mine DHPE	For CSLM study

MATERIALS AND CHEMICALS:

Etodolac was received as gift sample from Micro Labs Limited, Mumbai. Soya lecithin, Span 60, Tween 80, PEG 400, Triethanolamine, Carbopol 934, Glycerine, Disodium hydrogen phosphate (monobasic), Methanol and Ethanol were obtained from Research lab-fine chem industries. Sodium hydroxide was obtained from thermo fisher scientific India Pvt. Ltd. Dialysis membrane was obtained from membrane solutions.

PREFORMULATION STUDY:

Estimation of λ max and plot of calibration curve by UV-visible spectrophotometer:

Preparation of standard stock solution of drug (in Methanol):

Drug weighed and dissolved in methanol to obtain the concentration of 1000 ppm. This solution was used as a standard stock solution to obtain further dilutions.

Spectrophotometric scanning and determination of λ max of Etodolac (in Methanol):

From the stock solution, the UV-scan was taken between the wavelength ranges
200-400 nm and the highest peak in the spectra were further selected as the maximum wavelength for Etodolac.

Preparation of standard plot of Etodolac (in Methanol):

From the standard stock solution, dilutions of 200, 400, 600, 800, 1000 ppm solutions using methanol and absorbance were measured by using a UV spectrophotometer.

Preparation of PBS pH 7.4 (phosphate buffer saline):

Dissolve 13.61 of potassium hydroxide monobasic (KH2PO4) in 500 ml water in one volumetric flask. In another volumetric flask, dissolve 4 gm of sodium hydroxide in 500 ml distilled water to prepare 0.2 M NaOH. Add 50 ml of KH2PO4 solution in 200 ml volumetric flask and add 0.2 M NaOH solution.

Preparation of standard calibration curve of Etodolac in Phosphate buffer solution (pH 7.4):

Preparation of standard stock solution (in PBS pH 7.4):

The drug was weighed and dissolved in phosphate buffer pH 7.4 to obtain 1000 ppm. This solution was used as a standard stock solution to obtain further dilutions.

Spectrophotometric scanning of Etodolac (in PBS pH 7.4):

From the stock solution, the UV-scan was taken between 200-400 nm, and the highest peak in the spectra selected as the maximum wavelength for Etodolac.

Preparation of standard plot for Etodolac (in PBS pH 7.4):

From the stock solution, dilutions of 20, 40, 60, 80, and 100 ppm solutions were prepared using phosphate buffer pH 7.4, and absorbance was measured by using UV-spectrophotometer.

Drug-excipients compatibility study by Fourier Transform Infra-Red (FTIR):

The drug excipients study is done by FTIR spectroscopy. In this method, the IR spectrum of API and excipients and drug-excipients mixture were recorded by FTIR. The compatibility of drug and excipients was checked by comparing different spectrums obtained from FTIR studies [10].

FORMULATION OF TRANSFERSOMES SYSTEM:

Transfersomal formulation were prepared by using Etodolac, soya-lecithin, Span 60, Tween 80 and mixture of span 60 and tween 80 by thin film hydration method. Weighed amount of drug, phospholipid and surfactant was dissolved in organic solvent (Methanol: Ethanol) respectively and poured both solutions in clan and dry round bottom flask. Evaporation of solvent was done by Rotary flash evaporator for 30-40 min at 60rpm under reduced pressure above lipid transition temperature. Obtained thin lipid film was hydrated with PBS (pH 7.4) for 1 hr. at 60 rpm and was kept overnight for hydration [11,12,13].

SEPERATION OF UNENTRAPPED MATERIAL:

Dispersion was subjected to centrifugation. Before centrifugation methanol was added in dispersion in order to solubilize unentrapped drug. After centrifugation layer of entrapped drug and unentrapped drug (supernatant liquid) was separated. Further supernatant liquid was used for estimation of % unentrapped drug.

FORMULATION OF TRANSFERSOMAL GEL:

By dispersion method

Various concentration of Carbopol 934 was used to prepare gel base in which transfersomal system was added. Boil the water in a beaker and then add the weighed amount of Carbopol 943 (gelling agent). Stir

the solution continuously on a magnetic stirrer until Carbopol swells. Glycerin was added to that solution. Dissolve methylparaben and ethyl paraben in propyl glycol solution to Carbopol solution. Further, triethanolamine was added to neutralize the pH. Further gel was sonicated for 30 min (approx.) to remove entrapped drug [14].

Table 3: Composition of Transfersomal Gel.

Formulation Code	Carbopol 934	Propylene glycol	Glycerine
F1	0.5%	10%	5%
F2	1%	10%	5%
F3	1.5%	10%	5%

EVALUATION OF TRANSFERSOMAL GEL [14]:

Physical appearance: Developed transfersomal gel was evaluated for its colour, odour and its texture by visual inspection. Gel formulation also tested for floccules by visual inspection.

pH: pH of Transfersomal gel was measured by using digital pH meter. 20-30 gm of gel was placed in beaker and evaluated for ph. PH of prepared gel was found to be in the range of 7 to 7.6. Procedure carried out 3 times average of three readings was recorded.

Homogeneity: Prepared formulation was checked for presence of any floccule or sediment by visual inspection.

Spreadability: 1 gm was placed on the glass slide which is fixed on wooden block. Place a second slide on gel to which weight was attached. The thread was passed over the pulley whose one terminal was attached to slide while another was tied with weight.

$$s = (M \times L / T)$$

Where S denotes spreadability, M is the weight connected to the thread, L denotes the length of the glass slide, and T denotes the time taken to separate the slides (Mass and time should kept constant).

Viscosity: Viscosity of prepared gel was determined by Brookfield viscometer. Beaker containing 100 gm of gel was placed in Brookfield viscometer. T-bar spindle was dipped into gel to get viscosity. Viscosity was determined at different RPM.

Extrudability: The transfersomal gel formulation was filled in aluminium collapsible tube of capacity 10 gm. and sealed by crimping machine. Collapsible tube was placed between two slides on which weight of 500 gm. was placed. Amount of gel extruded was weighed and noted.

If Extrudability is,

1) >90% then it is excellent
2) >80% then it is good
3) >70% then it is fair

Percent drug content: 1 gm of formulated gel was transferred to 100 ml volumetric flask and make up volume by solvent. Suspension was sonicated in order to rupture the vesicles. Further dilution was prepared by filtering the suspension. Drug content was calculated by linear regression analysis method at 274 nm.

***In-vitro* diffusion study:** *In vitro* diffusion studies of prepared transfersomal gel were conducted with the help of Franz diffusion cell. Franz diffusion cell consist of two compartments i.e., donor compartment and receptor compartment. Vaseline was applied on inner edges (contact points of both compartment) and already soaked dialysis membrane was clamped between two compartments. Receptor compartment was filled with phosphate buffer solution (PBS) which was continuously stirred at 50 rpm and 37±1°c temperature. 1 gm of gel formulation was placed on diffusion membrane in donor compartment with PBS (Phosphate buffer solution) (pH 7.4). 1 ml sample were collected at different time interval and same amount of fresh medium was added. Diffusion of drug was determined by spectrophotometric analysis. Concentration of drug released was calculated by equation generated from standard calibration.

Drug Release Kinetics Modelling [15]:

Zero order model: $C0-Ct = K0\ t\ Ct = C0 + K0\ t$

Where Ct is the amount of drug released at time t, C0 denotes the drug's initial concentration at time t=0, and K0 denotes the zero-order rate constant.

First order model: $Log\ C = log\ C0 - k1\ t/2.303$

Where C is the percent of drug left at time t, C0 is the drug's initial concentration at time t=0, and K1 is the first order rate constant.

Higuchi model: $Q = KH\ t^{1/2}$

Where Q represents the total amount of medication released at time t, and KH represents the Higuchi dissolution constant.

Korsmeyer-Peppas model: Log (Mt/M∞) = log KKP + n log t

Where Mt represents the quantity of drug released at time t, M represents the amount of drug released after time t, and M represents the amount of drug released after time t.

KKP = Korsmeyer-Peppas model release rate constant, n = diffusional exponent or drug release exponent.

Hixson-Crowell model: W01/3-Wt1/3 = KHC t

Where W0 represents the initial amount of drug released at time t=0, Wt represents the leftover drug at time t, and KHC represents the Hixson-Crowell constant.

Stability studies:

On the basis of % entrapment efficiency and In-vitro drug release transfersomal gel formulation was selected for stability studies. Transfersomal formulations were kept at specified storage conditions as per ICH guidelines. At different time interval samples were withdrawn and evaluated for % entrapment efficiency and other parameters. The formulation which is retaining its parameter over the specified period was selected as stable formulation.

RESULTS ANS DISCUSSION:

Spectrophotometric scanning and determination of λ max of Etodolac (in methanol): spectrophotometric scanning of etodolac in methanol was performed in order to get λ max (wavelength maxima) of etodolac in methanol. λ max was found to be 274nm.

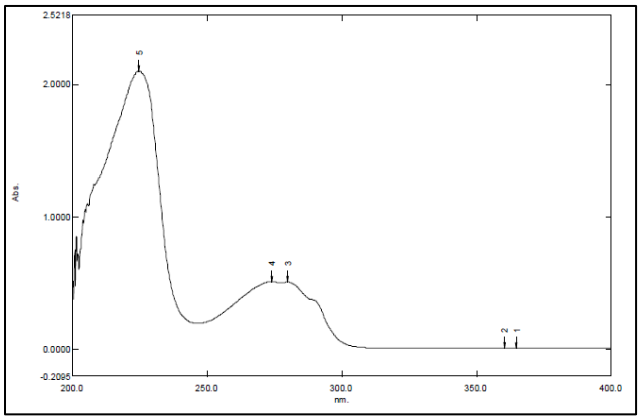

Figure 1: Absorption spectrum of Etodolac in methanol

Plotting of calibration curve of Etodolac (in methanol): Calibration curve of Etodolac was obtained by plotting a graph of conc. (µg/ml) vs absorbance's. The linear regression analysis of collected absorbance data point was done. The correlation coefficient (r^2) was found to be 0.9962.

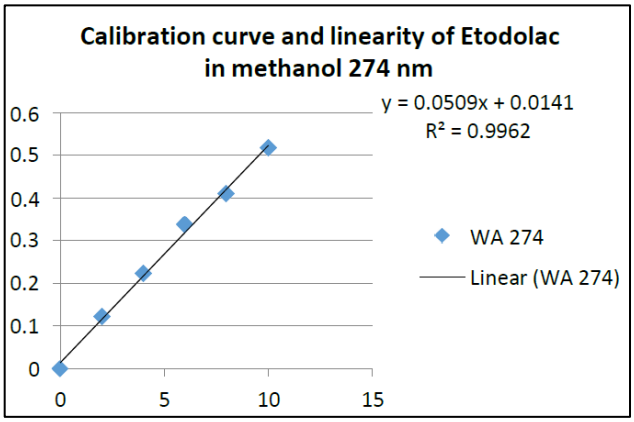

Figure 2: Calibration curve of etodolac in methanol

Spectrophotometric scanning and determination of λ max of Etodolac in PBS pH 7.4): spectrophotometric scanning of etodolac in PBS was performed in order to get λ max (wavelength maxima) of etodolac in PBS. λ max was found to be 274nm.

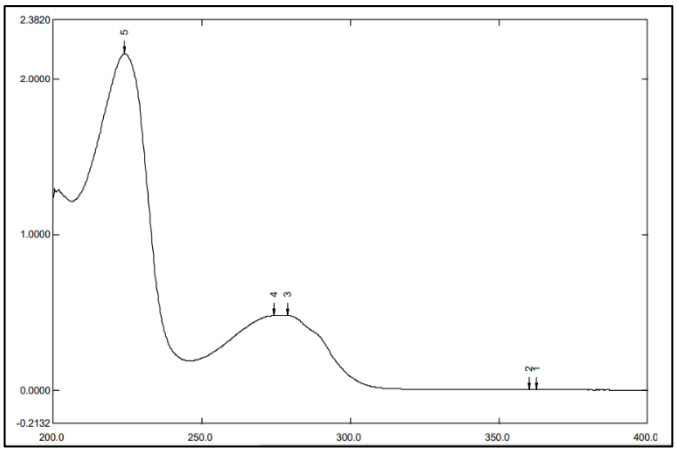

Figure 3: Absorption spectrum of Etodolac (in PBS pH 7.4)

Plotting of calibration curve of Etodolac (in PBS pH 7.4): Calibration curve of etodolac was obtained by plotting a graph of conc. (µg/ml) vs absorbance's. The linear regression analysis of collected absorbance data point was done. The correlation coefficient (r^2) was found to be 0.9988.

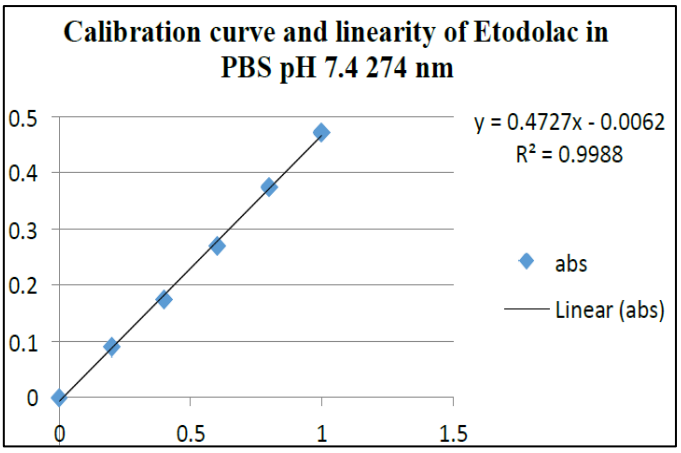

Figure 4: Calibration curve of Etodolac (in PBS pH 7.4)

Drug-excipients compatibility study by Fourier Transform Infra-Red (FTIR): The FTIR study of drug and other excipients was performed and then the mixture of drug with all excipients was performed to get drug-excipients compatibility study. Drug and other excipient were triturated to get uniform mixture.

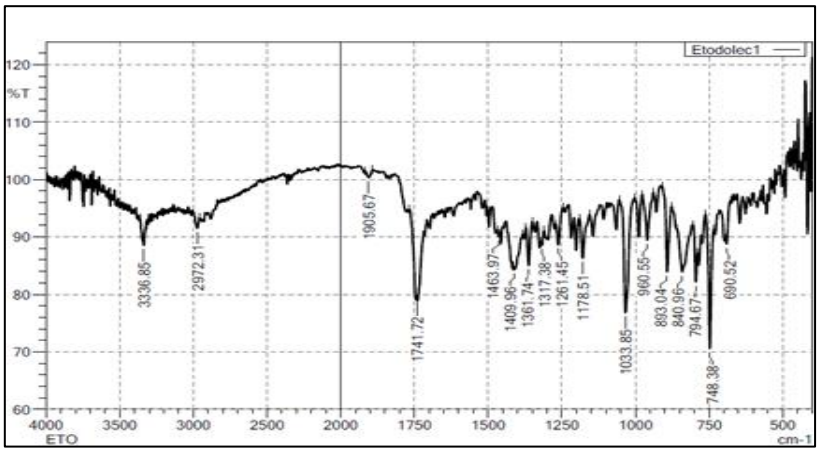

Figure 5: IR spectra of Etodolac

TRANSFERSOMAL GEL:

Prepared transfersomal gel was evaluated for different parameters such as Homogeneity, pH, Viscosity, Grittiness, Extrudability, Spreadability, Drug content uniformity and In-vitro diffusion. Further these parameters were placed in tabular for to get quick review.

Table 4: Evaluation parameter of Transfersomal gel

Formulation	**TG1**	**TG2**	**TG3**
Homogeneity	+++	+++	+++
pH	7.32±0.32	7.44±0.69	7.21±0.49
Viscosity (cP)	28,210±119	3,75,000±108	5,97,200±133
Spreadability (g.cm/sec)	87.4±3.86	82±3.47	72.5±4.79
Extrudability (%)	92.46±0.52%	90.33±0.64%	88.90±0.69%
Drug content uniformity (%)	94.5±0.21%	76.58±1.72%	85.9±1.21%
Skin irritation	No	No	No
*n (number of observations) = 03			
+++ Excellent, ++ Good, + Satisfactory, - Poor, -- Fail			

***In-vitro* diffusion:** All formulations were subjected to an 8-hour in-vitro diffusion investigation, during which the drug's diffusion was calculated. In-vitro drug release of all gels was studied utilising Frans-diffusion cell cellophane membrane. We may deduce from the findings that the TG1 formulation has a high drug release rate of 92.83 percent in 8 hours. Drug release is also good in TG2 and TG3. The data on drug release is presented in a tabular style below.

Table 5: In-vitro diffusion study

Time (hr.)	**TG1**	**TG2**	**TG3**
0 hr.	15.59 %	16.38 %	9.74 %
1 hr.	26.22 %	38.19 %	33.07 %
2 hr.	37.73 %	53.94 %	37.75 %
3 hr.	41.27 %	57.73 %	44.42 %
4 hr.	44.11 %	49.95 %	39.36 %
5 hr.	54.95 %	64.89 %	54.08 %
6 hr.	70 %	73.15 %	63.13 %
7 hr.	77.37 %	79.57 %	70.36 %
8 hr.	92.83 %	86.10 %	80.69 %

All the transfersomal gel was found to be homogeneous and Neutral.

In case of Spreadability, TG 1 was found to be good as compared to TG2 and TG3 and also no particulate matter was observed under optical microscope which ensure the requirement of freedom from particulate matter.

Extrudability of transfersomal gel 1 (TG1) was found to be good as compared to TG2 and TG3 formulations. The more the quantity of gel extruded from collapsible tube better is the Extrudability.

In case of drug content uniformity, TG1 formulation is showing uniform distribution of drug throughout the gel. All formulation passes the skin irritation test as none of them showing skin irritation to volunteers

Drug Release Kinetic Modelling:

The in-vitro release data was fitted in various kinetic model to predicts the release mechanism of drug from Transfersomal gel.

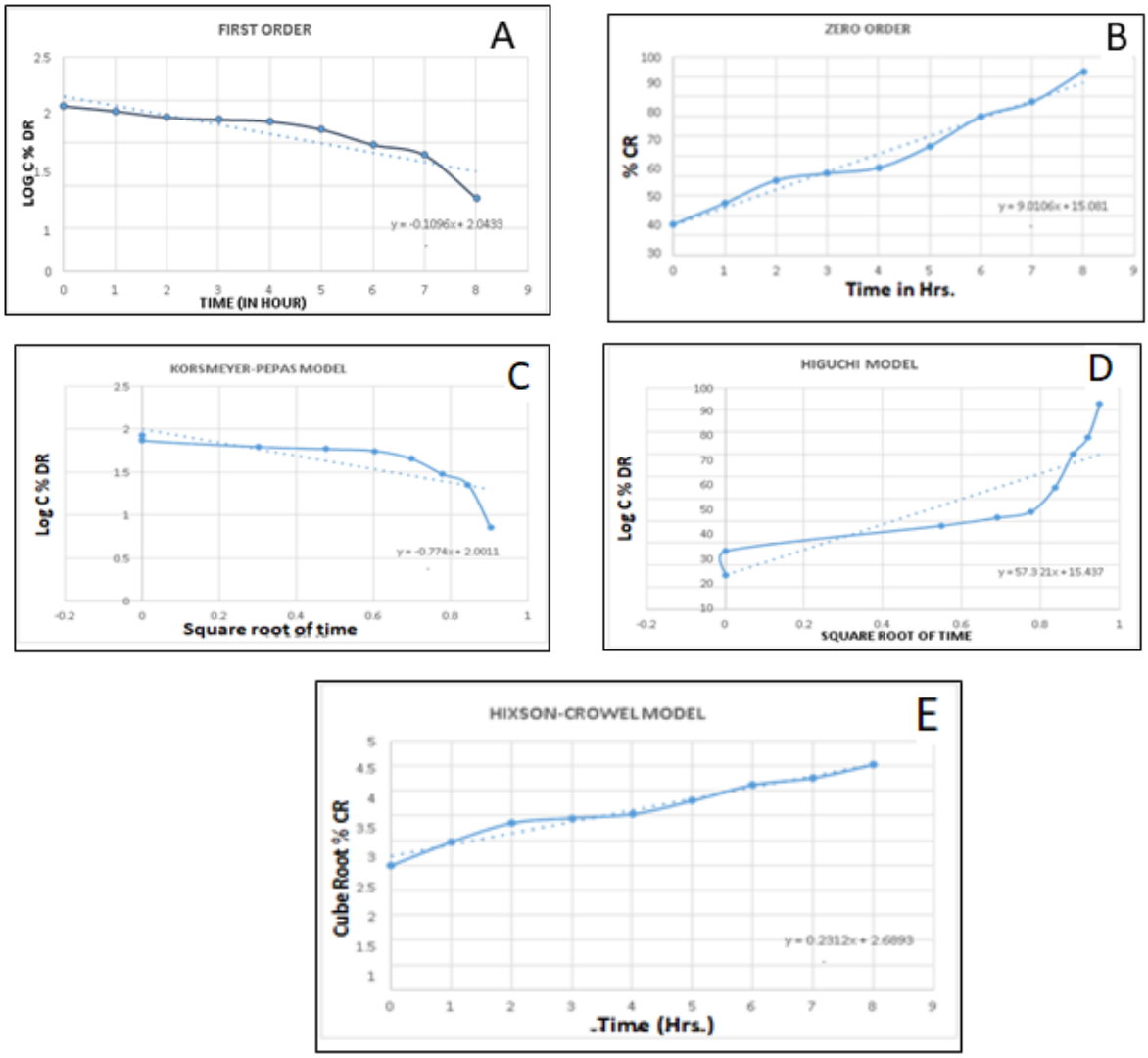

Figure 6: Drug release kinetics- A: First order; B: Zero order; C: Korsmeyer-Peppas model; D: Higuchi model; E: Hixon-Crowell model

For the TG 1 formulation, the zero Order formulation provided the greatest fit higher correlation around R2. We can infer that the formulation of TG 1 follows a zero-order release model.

Table 6: Regression analysis data of transfersomal gel formulation

Batch	First order model	Zero order model	Korsmeyer-Peppas model	Higuchi model	Hixson- Crowell model
TG 1	R2	R2	R2	R2	R2
	0.8012	0.9727	0.6315	0.733	0.9703

Stability Study:

Transfersomal gel formulation, containing of different % of carbomer was kept for stability studies as per specified storage conditions of ICH guidelines. At different interval of time, samples were withdrawn and were evaluated for its parameters. The formulation that retained its parameters according to the specified storage condition for over the period of three months was considered and selected as stable formulation.

Table 7: Stability study of Transfersomal gel

Formulation	TG1			TG2			TG3		
Storage condition: 30ºC ±2ºC/ 65 % RH ± 5% RH									
Time interval (days)	30 days	60 days	90 days	30 days	60 days	90 days	30 days	60 days	90 days
Homogeneity	+++	+++	+++	+++	+++	+++	++	++	++
pH	7.34 ±0.04	7.34 ±0.07	7.38 ±0.03	7.46 ±0.02	7.46 ±0.06	7.21 ±0.04	7.21 ±0.03	7.00 ±0.12	7.23 ±0.09
Spreadability (g.cm/sec)	87± 4.89	87± 3.89	87± 4.51	82± 3.44	82± 3.73	82± 3.13	72± 4.77	72± 4.34	72± 0.28
Extrudability (%)	92.46 ±0.39	92.46 ±0.53	92.46 ±0.37	90.33 ±0.75	90.33 ±0.67	90.33 ±0.81	88.90 ±0.31	88.90 ±0.43	88.90 ±0.61
Drug content Uniformity (%)	94.5 ±0.16	94.5 ±0.80	94.5 ±1.64	76.0 ±1.90	76.0 ±1.70	76.0 ±1.84	85 ±1.24	85 ±0.86	85 ±1.59
Skin irritation test	No	No	No	No	No	No	No	No	No
*n (number of observations) = 03									
+++ Excellent, ++ Good, + Satisfactory, - Poor, -- Fail									

TG1 retains almost all the properties when stored at specified storage conditions over the period of 90 days. TG2 and TG3 also retain all the properties but less as compared to TG 1. BY reviewing the tabular form, we can conclude that there is less variation in the properties of all the transfersomal gels indicating very much stable formulations.

CONCLUSION:

Transfersomal gel was formulated by thin film hydration method by using different concentrations of Tween 80, Span 60 and their mixture with Soya lecithin (Phospholipid). Further dispersions of these surfactant and phospholipid were loaded in the 0.5%, 1% and 1.5% Carbopol 934 to get gels. Transfersomal gel formulation of etodolac will helps to reduce unwanted and undesired side effects related to oral route. Transfersomal formulation could be more effective than oral formulation as they show faster drug release than oral formulation. Stability study and kinetics data revels that optimized formulation was stable at storage conditions and it follows zero order kinetics. The transfersomal gel formulation have immense potential and can be used for its clinical application in future.

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CONFLICT OF INTERESTS: Authors declare that there is no conflict of interest.

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